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QUESTIONS

1. Classify the antimalarial agents and state the mechanism of action of each class of drug listed

1. Antimalarial agents can be classified as follows:

CLASSIFICATION

1. 4-AMINOQUINOLINES: Chloroquine, Amodiaquine, Piperaquine.
2. QUINOLINE-METHANOL: Mefloquine.
3. CINCHONA ALKALOID: Quinine, Quinidine.
4. BIGUANIDE: Proguanil (Chloroguanide), Chlorproguanil.
5. DIAMINOPYRIMIDINE: Pyrimethamine.
6. 8-AMINOQUINOLINES: Primaquine, Bulaquine.
7. SULFONAMIDES AND SULFONE: Sulfadoxine, Sulfamethopyrazine, Dapsone.
8. ANTIBIOTICS: Tetracycline, Doxycycline.
9. SESQUITERPINE LACTONES: Artesunate, Artemether, Arteether.
10. AMINO ALCOHOLS: Halofantrine, Lumefantrine.
11. NAPHTHYRIDINE: Pyronaridine.
12. NAPHTHOQUINONE: Atovaquone.

MECHANISM OF ACTION

NO	CLASS	DRUG	MECHANISM OF ACTION
1	4-AMINOQUINOLINES	Chloroquine, Amodiaquine, Piperaquine.	Chloroquine and other similar quinolones (e.g. hydroxychloroquine, quinine) inhibits the action of heme polymerase in malarial trophozoites, preventing the conversion of heme to hemazoin. Plasmodium species continue to accumulate toxic heme, killing the parasite. Chloroquine passively diffuses through cell membranes and into endosomes, lysosomes, and Golgi vesicles; where it becomes protonated, trapping the chloroquine in the organelle and raising the surrounding pH. The raised pH in endosomes, prevent virus particles from utilizing their activity for fusion and entry into the cell.

2	QUINOLINE-METHANOL	Mefloquine	This class of drugs is chemically related to quinidine. Has strong blood schizonticidal activity against P. falciparum and P. vivax, but not against hepatic stages or gametocytes. Mefloquine produces swelling of the Plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components.
3	CINCHONA ALKALOID	Quinine, Quinidine	The mechanism of action for quinine and related anti-malarial drugs is that these drugs are toxic to the malaria parasite. Specifically, the drugs interfere with the parasite's ability to break down and digest hemoglobin. Consequently, the parasite starves and/or builds up toxic levels of partially degraded hemoglobin in itself.
4	BIGUANIDE	Proguanil (Chloroguanide), Chlorproguanil	Proguanil inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.
5	DIAMINOPYRIMIDINE	Pyrimethamine	Pyrimethamine interferes with the regeneration of tetrahydrofolic acid from dihydrofolate by competitively inhibiting the enzyme dihydrofolate reductase. Tetrahydrofolic acid is essential for DNA and RNA synthesis in many species, including protozoa.
6	8-AMINOQUINOLINES	Primaquine, Bulaquine	Primaquine's mechanism of action may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. Also, primaquine may bind to and alter the properties of protozoal DNA.
7	SULFONAMIDES AND SULFONE	Sulfadoxine, Sulfamethopyrazine, Dapsone.	Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling to, an area where there is a chance of getting malaria. Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-amino benzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism. All cells

			require folic acid for growth. Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.
8	ANTIBIOTICS	Tetracycline, Doxycycline	Tetracycline passively diffuses through porin channels in the bacterial membrane and reversibly binds to the 30S ribosomal subunit, preventing binding of tRNA to the mRNA-ribosome complex, and thus interfering with protein synthesis.
9	SESQUITERPINE LACTONES	Artesunate, Artemether, Arteether	The mechanism of artesunate is thought to involve cleavage of the endoperoxide bond through reaction with haeme. This produces free radicals which alkylate parasitic proteins. It has been shown to inhibit an essential parasite calcium adenosine triphosphatase enzyme. Artesunate inhibits malaria proteins EXP1, a glutathione S-transferase, responsible for breaking down cytotoxic hematin.
10	AMINO ALCOHOLS	Halofantrine, Lumefantrine	The mechanism of action of Halofantrine may be similar to that of chloroquine, quinine, and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite.
11	NAPHTHYRIDINE	Pyronaridine	Its mechanism of action similar to that of the well-known 4-aminoquinoline chloroquie, namely, it inhibits beta-hematin formation vitro (a process which closely parallels hemozoin formation within the parasite food vacuole), forms a drug-hematin complex, inhibits glutathione-dependent degradation of hematin, and enhances hematin-induced lysis of red blood cell but at 1/100 of the concentration seen with Chloroquine.
12	NAPHTHOQUINONE	Atovaquone	The mechanism of action against Pneumocystis carinii has not been fully elucidated. In Plasmodium species, the site of action appears to be the cytochrome bc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis. Atovaquone also has been shown to have good in vitro activity against Toxoplasma gondii.